Eisai Co., Ltd.
Public Relations:
+81-(0)3-3817-5120

Merck & Co., Inc., Kenilworth, N.J., U.S.A.
Media Relations
Pamela Eisele: (267) 305-3558
Rebecca Newberry: (484) 678-2952

Eisai Co., Ltd.
Investor Relations:
+81-(0)3-3817-3016

Merck & Co., Inc., Kenilworth, N.J., U.S.A.
Investor Relations
Peter Dannenbaum: (908) 740-1037
Courtney Ronaldo: (908) 740-6132

LENVIMA® (lenvatinib) Plus KEYTRUDA® (pembrolizumab) Demonstrated Superior Progression-Free Survival (PFS) and Overall Survival (OS) Versus Sunitinib as First-Line Treatment for Patients With Advanced Renal Cell Carcinoma

LENVIMA Plus KEYTRUDA Significantly Reduced Risk of Disease Progression or Death by 61% Versus Sunitinib, With a Median PFS of Nearly Two Years Versus Nine Months for Sunitinib

LENVIMA Plus Everolimus Significantly Improved PFS and Objective Response Rate Versus Sunitinib

First Results From Pivotal CLEAR Study (Study 307/KEYNOTE-581) Presented at 2021 Genitourinary Cancers Symposium (ASCO GU) and Published in the New England Journal of Medicine

TOKYO and KENILWORTH, N.J., Feb.15, 2021 – Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") and Merck & Co., Inc., Kenilworth, N.J., U.S.A. (known as MSD outside the United States and Canada) today announced the first presentation of new investigational data from the pivotal Phase 3 CLEAR study (Study 307/KEYNOTE-581) in an oral presentation session (Abstract #269) at the virtual 2021 Genitourinary Cancers Symposium (ASCO GU) and simultaneously published in *the New England Journal of Medicine*[1]. The trial evaluated the combinations of LENVIMA®, the orally available multiple receptor tyrosine kinase inhibitor discovered by Eisai, plus KEYTRUDA®, the anti-PD-1 therapy from Merck & Co., Inc., Kenilworth, N.J., U.S.A., and LENVIMA plus everolimus versus sunitinib for the first-line treatment of patients with advanced renal cell carcinoma (RCC). LENVIMA plus KEYTRUDA demonstrated statistically significant and clinically meaningful improvements in progression-free survival (PFS; HR=0.39 [95% CI: 0.32-0.49]; p<0.001), overall survival (OS; HR=0.66 [95% CI: 0.49-0.88]; p=0.005) and objective response rate (ORR; relative risk=1.97 [95% CI: 1.69-2.29]; p<0.001) versus sunitinib. LENVIMA plus everolimus also showed statistically significant improvements in PFS (HR=0.65

[95% CI: 0.53-0.80]; p<0.001) and ORR (relative risk=1.48 [95% CI: 1.26-1.74]; p<0.001) versus sunitinib. In an exploratory analysis, results for PFS and OS were consistent across prespecified Memorial Sloan Kettering Cancer Center (MSKCC) risk groups (favorable, intermediate and poor). Full MSKCC risk group data can be found in the *New England Journal of Medicine* article entitled "Lenvatinib Plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma," published. The safety profiles of both LENVIMA plus KEYTRUDA and LENVIMA plus everolimus were consistent with previously reported studies.

"Continued efforts to improve outcomes in patients with advanced renal cell carcinoma are critical, considering that the number of people diagnosed with the disease has more than doubled over the last 50 years, and almost one-third of these patients are diagnosed at an advanced stage," said Dr. Robert Motzer, Medical Oncologist, Kidney Cancer Section Head, Genitourinary Oncology Service, Memorial Sloan Kettering Cancer Center. "KEYTRUDA plus LENVIMA demonstrated a median progression-free survival of nearly two years, and seven in 10 patients experienced an objective response. This combination also significantly improved overall survival compared with sunitinib, with a 34% reduction in risk of death. These results suggest that this combination has the potential to impact clinical practice for this type of devastating cancer."

In the trial's primary endpoint of PFS, as assessed by independent review per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, LENVIMA plus KEYTRUDA reduced the risk of disease progression or death by 61% (HR=0.39 [95% CI: 0.32-0.49]; p<0.001), with a median PFS of 23.9 months (95% CI: 20.8-27.7) versus 9.2 months (95% CI: 6.0-11.0) for patients who received sunitinib. In the trial's key secondary endpoints, LENVIMA plus KEYTRUDA reduced the risk of death by 34% (HR=0.66 [95% CI: 0.49-0.88]; p=0.005) versus patients who received sunitinib. Median OS was not reached in either treatment arm after a median follow-up of 27 months. Treatment with LENVIMA plus KEYTRUDA resulted in an ORR of 71.0% (95% CI: 66.3-75.7), with a complete response (CR) rate of 16.1% and a partial response (PR) rate of 54.9%, versus an ORR of 36.1% (95% CI: 31.2-41.1), with a CR rate of 4.2% and a PR rate of 31.9%, for patients who received sunitinib (relative risk=1.97 [95% CI: 1.69-2.29]; p<0.001). Median duration of response (DOR) for patients who received LENVIMA plus KEYTRUDA was 25.8 months (95% CI: 22.1-27.9) versus 14.6 months (95% CI: 9.4-16.7) for patients who received sunitinib.

"These promising results are a testament to our company's commitment to help improve outcomes for patients diagnosed with cancer," said Dr. Gregory Lubiniecki, Vice President,

Oncology Clinical Research, Merck & Co., Inc., Kenilworth, N.J., U.S.A. Research Laboratories. “In this trial, KEYTRUDA plus LENVIMA demonstrated superior efficacy benefits compared with sunitinib. If approved, we believe this combination has the potential to be an important new treatment option for patients with advanced renal cell carcinoma in the first-line setting.”

In the trial’s second experimental treatment arm, LENVIMA plus everolimus reduced the risk of disease progression or death by 35% (HR=0.65 [95% CI: 0.53-0.80]; p<0.001), with a median PFS of 14.7 months (95% CI: 11.1-16.7) versus 9.2 months (95% CI: 6.0-11.0) for patients who received sunitinib. LENVIMA plus everolimus did not demonstrate an improvement in OS compared with sunitinib (HR=1.15 [95% CI: 0.88-1.50]; p=0.3). Median OS was not reached in either treatment arm after a median follow-up of 27 months. The ORR was 53.5% (95% CI: 48.3-58.7), with a CR rate of 9.8% and a PR rate of 43.7%, for patients who received LENVIMA plus everolimus versus 36.1% (95% CI: 31.2-41.1), with a CR rate of 4.2% and a PR rate of 31.9%, for patients who received sunitinib (relative risk=1.48 [95% CI: 1.26-1.74]; p<0.001). Median DOR for patients who received LENVIMA plus everolimus was 16.6 months (95% CI: 14.6-20.6) versus 14.6 months (95% CI: 9.4-16.7) for patients who received sunitinib.

“These investigational data from the CLEAR study (Study 307/KEYNOTE-581) represent a significant milestone in our clinical research efforts in advanced renal cell carcinoma, with encouraging Phase 3 results in this population for the LENVIMA plus KEYTRUDA combination and with more than 700 patients having received LENVIMA plus everolimus in the clinical trial setting” said Dr. Takashi Owa, Vice President, Chief Medicine Creation and Chief Discovery Officer, Oncology Business Group at Eisai. “Our progress thus far also reflects the significant contributions of dedicated patients, healthcare staff and researchers who continued to support this study during the global pandemic, to whom we extend our deepest gratitude.”

In the LENVIMA plus KEYTRUDA arm, treatment-related adverse events (TRAEs) led to discontinuation of LENVIMA in 18.5% of patients, of KEYTRUDA in 25.0% of patients, and of both in 9.7% of patients. In the LENVIMA plus everolimus arm, TRAEs led to discontinuation of LENVIMA in 16.1% of patients, of everolimus in 19.2% of patients, and of both in 13.5% of patients. In the sunitinib arm, TRAEs led to discontinuation of sunitinib in 10.0% of patients. Grade 5 TRAEs occurred in 1.1% of patients in the LENVIMA plus KEYTRUDA arm and 0.8% of patients in the LENVIMA plus everolimus arm, versus 0.3% of patients in the sunitinib arm. Grade ≥3 TRAEs occurred in 71.6% of patients in the LENVIMA plus KEYTRUDA arm, in 73.0% of patients in the

LENVIMA plus everolimus arm, and in 58.8% of patients in the sunitinib arm. The most common TRAEs of any grade occurring in at least 20% of patients in the LENVIMA plus KEYTRUDA arm were diarrhea (54.5%), hypertension (52.3%), hypothyroidism (42.6%), decreased appetite (34.9%), fatigue (32.1%) and stomatitis (32.1%). In the LENVIMA plus everolimus arm, the most common TRAEs of any grade occurring in at least 20% of patients were diarrhea (59.7%), stomatitis (45.6%), hypertension (43.1%), fatigue (36.6%), decreased appetite (34.9%) and proteinuria (31.8%). In the sunitinib arm, the most common TRAEs of any grade occurring in at least 20% of patients were diarrhea (44.4%), hypertension (39.1%), stomatitis (37.4%), hand-foot syndrome (35.9%), fatigue (32.1%) and nausea (27.6%).

About the CLEAR Study (Study 307/KEYNOTE-581)

The CLEAR Study (Study 307/KEYNOTE-581) is a Phase 3, multi-center, randomized, open-label trial (ClinicalTrials.gov, NCT02811861) evaluating LENVIMA in combination with KEYTRUDA or in combination with everolimus versus sunitinib for the first-line treatment of patients with advanced RCC. The primary endpoint is PFS by independent review per RECIST v1.1. Key secondary endpoints include OS, ORR and safety. A total of 1,069 patients were randomized to one of three treatment arms to receive LENVIMA (20 mg orally once daily) in combination with KEYTRUDA (200 mg intravenously every three weeks); or LENVIMA (18 mg orally once daily) in combination with everolimus (5 mg orally once daily); or sunitinib (50 mg orally once daily for four weeks on treatment, followed by two weeks off treatment).

About Renal Cell Carcinoma (RCC)

Worldwide, it is estimated there were more than 430,000 new cases of kidney cancer diagnosed and nearly 180,000 deaths from the disease in 2020.[2] In Japan, there were more than 25,000 new cases and 8,000 deaths in 2020.[3] In the U.S. alone, it is estimated there will be more than 76,000 new cases of kidney cancer diagnosed and nearly 14,000 deaths from the disease in 2021.[4] Renal cell carcinoma is by far the most common type of kidney cancer; about nine out of 10 kidney cancers are RCCs.[4] Renal cell carcinoma is about twice as common in men as in women.[4] Most cases of RCC are discovered incidentally during imaging tests for other abdominal diseases. Approximately 30% of patients with RCC will have metastatic disease at diagnosis, and as many as 40% will develop metastases after primary surgical treatment for localized RCC.[5,6] Survival is highly dependent on the stage at diagnosis, and with a five-year survival rate of 12% for metastatic disease, the prognosis for these patients is poor.[7]

About LENVIMA® (lenvatinib) Capsules

LENVIMA, discovered and developed by Eisai, is a kinase inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). LENVIMA inhibits other kinases that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF) receptors FGFR1-4, the platelet derived growth factor receptor alpha (PDGFRα), KIT, and RET. In syngeneic mouse tumor models, lenvatinib decreased tumor-associated macrophages, increased activated cytotoxic T cells, and demonstrated greater antitumor activity in combination with an anti-PD-1 monoclonal antibody compared to either treatment alone. The combination of LENVIMA and everolimus showed increased anti-angiogenic and anti-tumor activity as demonstrated by decreased human endothelial cell proliferation, tube formation, and VEGF signaling in vitro and tumor volume in mouse xenograft models of human renal cell cancer greater than each drug alone. Currently, LENVIMA has been approved for monotherapy as a treatment for thyroid cancer in over 70 countries including Japan, the United States, in Europe, China and in Asia, and for unresectable hepatocellular carcinoma in over 65 countries including Japan, the United States, in Europe, China and in Asia. Additionally, it is also approved in combination with everolimus as a treatment for renal cell carcinoma following prior antiangiogenic therapy in over 60 countries, including the United States, in Europe and Asia. In Europe, the agent was launched under the brand name Kisplyx® for renal cell carcinoma. In addition, it is approved in combination with KEYTRUDA as a treatment for advanced endometrial cancer that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation in over 10 countries including the United States, Canada and Australia. Continued approval for this indication is contingent upon verification and description of clinical benefit in the confirmatory trials.

About KEYTRUDA® (pembrolizumab) Injection, 100mg

KEYTRUDA is an anti-PD-1 therapy that works by increasing the ability of the body's immune system to help detect and fight tumor cells. KEYTRUDA is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2, thereby activating T lymphocytes which may affect both tumor cells and healthy cells.

Merck & Co., Inc., Kenilworth, N.J., U.S.A. has the industry's largest immuno-oncology clinical research program. There are currently more than 1,300 trials studying KEYTRUDA across a wide variety of cancers and treatment settings. The KEYTRUDA clinical program seeks to

understand the role of KEYTRUDA across cancers and the factors that may predict a patient's likelihood of benefitting from treatment with KEYTRUDA, including exploring several different biomarkers.

About the Merck & Co., Inc., Kenilworth, N.J., U.S.A. and Eisai Strategic Collaboration

In March 2018, Eisai and Merck & Co., Inc., Kenilworth, N.J., U.S.A., known as MSD outside the United States and Canada, through an affiliate, entered into a strategic collaboration for the worldwide co-development and co-commercialization of LENVIMA. Under the agreement, the companies will jointly develop, manufacture and commercialize LENVIMA, both as monotherapy and in combination with KEYTRUDA, the anti-PD-1 therapy from Merck & Co., Inc., Kenilworth, N.J., U.S.A.

In addition to ongoing clinical studies evaluating the LENVIMA plus KEYTRUDA combination across several different tumor types, the companies have jointly initiated new clinical studies through the LEAP (LEnvatinib And Pembrolizumab) clinical program and are evaluating the combination in 14 different tumor types (endometrial carcinoma, hepatocellular carcinoma, melanoma, non-small cell lung cancer, renal cell carcinoma, squamous cell carcinoma of the head and neck, urothelial cancer, biliary tract cancer, colorectal cancer, gastric cancer, glioblastoma, ovarian cancer, pancreatic cancer and triple-negative breast cancer) across 20 clinical trials.

Eisai’s Focus on Cancer

Eisai focuses on the development of anticancer drugs, targeting the tumor microenvironment (with experience and knowledge from existing in-house discovered compounds) and the driver gene mutation and aberrant splicing (leveraging RNA Splicing Platform) as areas (*Ricchi*) where real patient needs are still unmet, and where Eisai can aim to become a frontrunner in oncology. Eisai aspires to discover innovative new drugs with new targets and mechanisms of action from these *Ricchi*, with the aim of contributing to the cure of cancers.

About Eisai

Eisai is a leading global research and development-based pharmaceutical company headquartered in Japan, with approximately 10,000 employees worldwide. We define our corporate mission as “giving first thought to patients and their families and to increasing the benefits health care provides,” which we call our *human health care* (*hhc*) philosophy. We strive to realize our *hhc* philosophy by delivering innovative products in therapeutic areas with high unmet medical needs, including Oncology and Neurology. In the spirit of *hhc*, we take that

commitment even further by applying our scientific expertise, clinical capabilities and patient insights to discover and develop innovative solutions that help address society's toughest unmet needs, including neglected tropical diseases and the Sustainable Development Goals.

For more information about Eisai, please visit www.eisai.com (for global), us.eisai.com (for U.S.) or www.eisai.eu (for Europe, Middle East, Africa), and connect with us on Twitter (U.S. and global) and LinkedIn (for U.S.).

Merck & Co., Inc., Kenilworth, N.J., U.S.A.'s Focus on Cancer

Our goal is to translate breakthrough science into innovative oncology medicines to help people with cancer worldwide. At Merck & Co., Inc., Kenilworth, N.J., U.S.A., the potential to bring new hope to people with cancer drives our purpose and supporting accessibility to our cancer medicines is our commitment. As part of our focus on cancer, Merck & Co., Inc., Kenilworth, N.J., U.S.A. is committed to exploring the potential of immuno-oncology with one of the largest development programs in the industry across more than 30 tumor types. We also continue to strengthen our portfolio through strategic acquisitions and are prioritizing the development of several promising oncology candidates with the potential to improve the treatment of advanced cancers. For more information about our oncology clinical trials, visit www.merck.com/clinicaltrials.

About Merck & Co., Inc., Kenilworth, N.J., U.S.A.

For more than 130 years, Merck & Co., Inc., Kenilworth, N.J., U.S.A., known as MSD outside of the United States and Canada, has been inventing for life, bringing forward medicines and vaccines for many of the world's most challenging diseases in pursuit of our mission to save and improve lives. We demonstrate our commitment to patients and population health by increasing access to health care through far-reaching policies, programs and partnerships. Today, Merck & Co., Inc., Kenilworth, N.J., U.S.A. continues to be at the forefront of research to prevent and treat diseases that threaten people and animals – including cancer, infectious diseases such as HIV and Ebola, and emerging animal diseases – as we aspire to be the premier research-intensive biopharmaceutical company in the world. For more information, visit www.merck.com and connect with us on Twitter, Facebook, Instagram, YouTube and LinkedIn.

Forward-Looking Statement of Merck & Co., Inc., Kenilworth, N.J., USA

This news release of Merck & Co., Inc., Kenilworth, N.J., USA (the "company") includes "forward-looking statements" within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs

and expectations of the company's management and are subject to significant risks and uncertainties. There can be no guarantees with respect to pipeline products that the products will receive the necessary regulatory approvals or that they will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of the global outbreak of novel coronavirus disease (COVID-19); the impact of pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the company's ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the company's patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

The company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in the company's 2019 Annual Report on Form 10-K and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site (www.sec.gov).

[1] Motzer R. et al. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. *The New England Journal of Medicine*

[2] International Agency for Research on Cancer, World Health Organization. "Kidney Fact Sheet." Cancer Today, 2020. https://gco.iarc.fr/today/data/factsheets/cancers/29-Kidney-fact-sheet.pdf .

[3] International Agency for Research on Cancer, World Health Organization. "Japan Fact Sheet." Cancer Today, 2020. https://gco.iarc.fr/today/data/factsheets/populations/392-japan-fact-sheets.pdf .

[4] American Cancer Society. Key Statistics About Kidney Cancer, https://www.cancer.org/cancer/kidney-cancer/about/key-statistics.html.

[5] Thomas A. Z. et al. The Role Of Metastasectomy In Patients With Renal Cell Carcinoma With Sarcomatoid Dedifferentiation: A Matched Controlled Analysis. *The Journal of Urology*. 2016 Sep; 196(3): 678–684. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5014677/pdf/nihms773463.pdf .

[6] Shinder B. et al. Surgical Management of Advanced and Metastatic Renal Cell Carcinoma: A Multidisciplinary Approach. *Frontiers in Oncology*. 2017; 7: 107. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5449498/#__ffn_sectitle .

[7] Padala, S. A., Barsouk, A., Thandra, K. C., Saginala, K., Mohammed, A., Vakiti, A., Rawla, P., & Barsouk, A. (2020). Epidemiology of Renal Cell Carcinoma. *World journal of oncology*, 11(3), 79–87. https://doi.org/10.14740/wjon1279 .

# # #